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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,870	07/23/2003	Howard J. Jacob	650053.00002	8005

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,870	JACOB ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' election with traverse of the invention of Group II, claims 11 and 12, drawn to a method of evaluating the effect of a test compound on diabetes and diabetic nephropathy, in the paper filed on 12/19/2005 is acknowledged. No arguments were given for the traversal.

Claims 1-10 and 13-15 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 11 and 12 are pending.

Claim Rejections - 35 USC § 112 – written description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601,

1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

When the claim is analyzed in light of the specification, the compound can be any compound that has an effect on diabetic nepropathy (p. 16, paragraph 0052). The specification discloses that the agent is not particularly limited by its structure or mode of action (p. 16, paragraph 0057), therefore it can be any compound that has the above mentioned effect. The genus, i.e., the agent, is described by its function to affect diabetic nephropathy, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different agents. It is acknowledged that some of the prior art provides examples of compounds identified through screening methods in animals, but no prior art discloses that by using one model one has possession of the whole genus.

In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicants invented what was claimed. Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

Claim Rejections - 35 USC § 112 - enablement

4. Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a rat model obtained by crossing Fawn Hooded rats with GK rats in a method of evaluating the effect that a test compound has on progression of diabetes and diabetic nephropathy in that particular rat, does not reasonably provide enablement for a method of evaluating the effect that a test compound has on diabetes and diabetic nephropathy, i.e., alleviating symptoms associated with type II diabetes in general, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims 11 and 12 are drawn to a method of identifying compounds that have an effect on diabetes and diabetic nephropathy. Such language directed to identify compounds that have an effect on diabetes and diabetic nephropathy is considered to embrace identifying a compound efficient enough such that, when administered to a subject, the treatment of the subject having a condition associated with the compound is achieved. Accordingly, preamble language directed to "evaluating

a test compound that has an effect on diabetes and diabetic nephropathy" is considered to require support as outlined in 35 U.S.C. § 112 first paragraph such that therapeutic benefit is considered to be enabled for one seeking to make and use such an evaluating method.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Breadth of the Claims

The instant claims 11 and 12 are drawn to method of evaluating the effect of a test compound on diabetes and diabetic nephropathy by using a rat diabetes model that develops symptoms of type II diabetes and progressive proteinuria and glomerulosclerosis leading to diabetic nephropathy in the absence of the test compound.

The aspect considered broad is the range of yet-to-be identified compounds that have an effect on diabetes and diabetic nephropathy. As will be shown below, this

broad aspect is not enabled.

The Nature of the Invention

The nature of the invention is the use of rat models of type II diabetes to identify compounds with an effect on diabetic symptoms and diabetic nephropathy. Such invention has use in the art for discovery of therapeutic agents to treat type II diabetes and complications associated with it.

However, the nature of such invention is within the broad genera of diabetes treatment, and diabetes treatment does not generally enable Applicants' invention due to problems with the complexity and unpredictability of this disorder. Susceptibility and outcome in complex disorders such as diabetes and its complications, such as diabetic nephropathy, are determined, at least in part by genetic polymorphism, and considerable difficulties remain in elucidating how many genes determine a particular phenotype. The etiology of the disease is multifactorial, and it is likely to involve the actions of genes at multiple levels along the multistage process that lead to diabetes. Van Tilburg et al. (J Med Genet, 2001, 38: 569-578) teach:

> "Unlike single gene disorders, where expression of the disease is influenced by a mutant allele at one gene locus, in common diseases like type 2 diabetes mellitus the disease expression depends on many gene loci which all have small to moderate effects. Type 2 diabetes mellitus is a so-called multifactorial disease in which the gene loci not only interact with each other but also with environmental factors.

With respect to the multifactorial nature of diabetic nephropathy, Barnas et al. (Diabetologia, 1997, 40: 327-331) teach:

> "Diabetic nephropathy develops in about 30% of patients with insulin-dependent diabetes mellitus (IDDM). The pathogenesis is considered to be multifactorial and genetic, and other factors such as metabolic control and haemodynamic alterations resulting in systemic and intrarenal hypertension might also contribute.

How will therapeutic apply in these cases? A multifactorial disease such as diabetes and its complications may require more than one agent for regulation. The use of single compounds may often not work very well, due to the complexity of regulatory pathways.

Given these teachings, one skilled in the art would not know what compound or combination of compounds to use to treat a clinical syndrome caused by mutations in a number of different genes. Along these lines, Keith et al. (Nature Reviews Drug discovery, 2005, 4: 71-78) teach:

> For most human diseases, there are no magic bullets. The more we learn about the genomic and molecular underpinnings of disease processes, the more apparent this conclusion becomes. Many diseases with a high incidence in the population, such as diabetes, heart disease, cancer, arthritis, asthma and depression, have a multifactorial basis that involves both genetic and environmental risk factors."

Hence, from the nature of the invention, the Artisan would not reasonably predict that the compound identified by the claimed method could be used to treat diabetes and diabetic nephropathy.

The State of the Prior Art and the Level of Predictability in the Art

Applicant contemplates to use a rat model that develops symptoms of type II diabetes in a method of evaluating the effect that a test compound has on progression of diabetes and diabetic nephropathy The problems with animal-based screening methods for therapeutic compounds are well known in the art, particularly with regard to forecasting aspects such as predicting the clinical response for the identified compounds. Such animal models have the potential to be misleading, as the molecular

pathways important for diabetes development in these models may be different from those in humans. For example, Kusminski et al. (Clinical Science, 2005, 109: 243-256) teach:

> "Resistin is a member of a class of cysteine-rich proteins collectively termed resistin-like molecules. Resistin has been implicated in the pathogenesis of obesity-mediated insulin resistance and T2DM, at least in rodent models.
>
> Recent studies have shed more light on differences between rodents and humans, indicating the diversity of resistin action in these species. Further studies are required to establish the relevance of resistin in human diabetes."

Reviewing the state of the art of animal research in diabetes mellitus Roep et al. (Diabetologia, 2004, 47: 1650-1656), teach:

> "Animal models have, over time, proved to be more often inaccurate than accurate, especially with regard to therapeutic interventions. Animal models should be used to study specific aspects of the disease process, and not considered to represent the clinical disease."

Given these teachings, one of skill in the art would not know that a compound identified by the instant method would necessarily have an effect on the human disease that can be caused by mutations in a number of different genes that are not important for the development of the disease in rats. How would one of skill in the art predict that the claimed method would render compounds that have an effect on diabetes and diabetic nephropathy as broadly claimed? Identification of a putative compound in an animal model is not an indication that the same compound will have an effective activity in humans. How does the effect that a test compound has on diabetic symptoms in a rat model correlate with a therapeutic effect in humans? The specification does not provide examples.

Therefore, at the time the instant invention was made, the use of animal models to identify compounds that modulate diabetes and diabetic nephropathy was a highly unpredictable art due to obstacles that continue to hinder the use of such methods in general. Such obstacles include, for example, problems with creating the animal models and predicting the clinical response.

Given these teachings, the skilled artisan would not know *a priori* whether the instant method, as broadly claimed, would render a compound capable of modulating cancer. One of skill in the art would not know how to use such a compound in such a way that would ensure efficient diabetes modulation.

Given this unpredictability, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant method to identify an enormous number of compounds as broadly or generically claimed, with a resultant identification of agents that have an effect on diabetes and diabetic nephropathy.

The Amount of Direction or Guidance/The Existence of Working Examples/ The Amount of Experimentation Necessary

The specification discloses only one example drawn to generation and characterization of a rat model obtained by crossing Fawn Hooded rats with GK rats. However, the specification does not provide examples of using this model to evaluate compounds on their effect on diabetes and diabetic nephropathy. The specification discloses several broad classes of possible compounds with possible effects on diabetic nephropathy (e.g., angiotensin II receptor antagonists, converting enzyme inhibitors,

TGFβ antagonists and antibodies, growth factor inhibitors, PPAR receptor agonists, antihypertensive agents, insulin sensitizing drugs, etc.), however, the specification does not discloses working examples identifying one of them as a compound that has an effect on diabetic nephropathy in a diabetic animal or human. This is a very broad range that includes compounds with different mechanisms of action and pharmacokinetics, therefore the outcome of using these compounds is unpredictable. The specification as filed is not enabling for the claimed invention because the specification as filed does not teach the usefulness of these agents as antihyperglycemic agents in animal models or humans. Thus, the issue is whether or not such a claimed assay could have been practiced by a person skilled in the art without undue experimentation, at the time the invention was made. How would we know that an agent showing an effect in an animal model is effective to treat the human disease? The specification does not provide guidance as to how to select for a hypoglycemic agent that can be used to treat human diabetes mellitus.

Therefore, the specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using animal models to identify proteins that can modulate diabetes and diabetic nephropathy. The field of using animal models to identify potential diabetes therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed identification methods.

Given the diverse and unpredictable outcome of using the disclosed method of identifying diabetes modulatory compounds, the specification does not appear to

provide sufficient guidance and/or working examples that specifically address the use of this method as being effective in identifying such compounds to enable one of ordinary skill in the art to use such identification method without undue experimentation.

Conclusion

In conclusion, the presently claimed invention only provides enough of a disclosure to allow for an artisan to test the effect of compounds on type 2 diabetes using a diabetes mellitus rat model obtained by crossing Fawn Hooded rats with GK rats and is therefore enabled for the part of the claimed invention that addresses using testing for a compound that ameliorates the symptoms of diabetes and diabetic nephropathy in this particular model, and not ameliorating symptoms associated with type II diabetes in general, as broadly claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (Diabetes, 1997, 46: 895-899), as evidenced by Kawano et al. (Diabetes Research and Clinical Practice, 1994, 24 Suppl: S317-S320).

Nakamura et al. teach evaluating the effect of a test compound, OPB-9195, on the development of diabetic nephropathy in OLETF rats (p. 896, column 1, second

paragraph). Nakamura et al. teach that OPB-9195 prevents the development of diabetic nephropathy when administered to the OLETF rats (p. 895, column 2, second paragraph, p. 898, column 1, second paragraph). The OLETF rats have been identified by the prior art as a good model for the human disease since it develops symptoms of type 2 diabetes and progressive nephropathy with nodule formation that resemble the human Kimmelstein-Wilson kidney (Kawano et al.). Therefore, the limitation of using a rat that develops symptoms of type 2 diabetes and progressive nephropathy with nodule formation is inherent in the prior art reference. Since the art teaches evaluating a test compound effect on diabetes and diabetes nephropathy in a rat model, wherein the rat would develop diabetic nephropathy in the absence of the test compound, the claimed invention is anticipated by the above cited art.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura et al., in view of Sone et al. (TRENDS in Molecular Medicine, 2001, 7: 320-322).

Nakamura et al. do not teach using a rat with symptoms of type 2 diabetes that has been genetically altered. Sone et al. teach knockout mice lacking the insulin

receptor substrate gene (p. 320, column 2, last paragraph). Sone et al. do not teach a transgenic rat. It would have been obvious for one skilled in the art, at the time the invention was made, to modify the rat of Nakamura et al., as taught by Sone et al., with a reasonable expectation of success. The motivation to do so is provided by Sone et al. who teach that the usefulness of targeting genes to produce animal models of type 2 diabetes in order to clarity the complicated pathophysiology of this disease (p. 320, column 1, second paragraph). One of skill in the art would have had a reasonable expectation of success in making such a model because it has been shown that such an animal model can be made and it can be used to decipher pathways important in development of type 2 diabetes. Thus, the claimed invention is prima facie obvious at the time the invention was made.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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